UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte EUGEN KOREN and MIRNA KOSCEC

Appeal No. 2004-2138
Application No. 08/765,324

ON BRIEF

Before MILLS, GRIMES, and GREEN, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 48-51, all of the claims remaining. Claims 48-51 read as follows:

48. A method for making antibodies to an epitope of a lipoprotein which reacts with the lipoprotein independently of lipid content and conformation of the lipoprotein, comprising

immunizing an animal with a desired apolipoprotein or lipoprotein which is delipidated, reduced, carboxymethylated, and solubilized with a reducing or denaturing agent, wherein all self-aggregated and degraded material has been removed from the delipidated, reduced, carboxymethylated, and solubilized apolipoprotein or lipoprotein.

49. The method of claim 48 further comprising

isolating the spleen from the immunized animals,

producing hybridomas from the spleen, and

screening the hybridomas for binding to the desired apolipoprotein or lipoprotein.

50. The method of claim 49 for making antibodies to a desired apolipoprotein wherein the apolipoprotein is selected from the group consisting of Apo AI, Apo AII, Apo B, Apo CIII, and Apo E.

51. The method of claim 49 for making antibodies to a lipoprotein wherein the lipoprotein is selected from the group consisting HDL, LDL, and VLDL.

The examiner relies on the following reference:

Lee et al. (Lee), "Properties of apolipoprotein B in urea and in aqueous buffers: The use of glutathione and nitrogen in its solubilization," Biochimica et Biophysica Acta, Vol. 666, pp. 133-146 (1981)

Claims 48-51 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking an adequate written description in the specification.

We reverse and enter new grounds of rejection of the claims on appeal.

Background

Lipoproteins are classified according to their density; the classes of lipoproteins include very low density lipoproteins (VLDL), low density lipoproteins (LDL), and high density lipoproteins (HDL). Specification, page 1. Lipoproteins contain, among other things, proteins known as apolipoproteins. There are four groups of apolipoproteins: A, B, C, and E (or Apo A, Apo B, Apo C, and Apo E, respectively). Page 2. Each of these groups comprises at least two different proteins; for example, the Apo A group includes the proteins Apo A-I, Apo A-II, and Apo A-IV, and the Apo B group includes the proteins Apo B-100 and Apo B-48. Id.

Each of the classes of lipoproteins (LDL, HDL, etc.) in turn includes different apolipoproteins in different proportions. LDL includes only Apo B-100 as its protein component, although Apo B-100 is also present in VLDL and intermediate density lipoproteins (IDL). By contrast, approximately 90% of the apolipoprotein in HDL is Apo A-I or Apo A-II, while apolipoproteins in the Apo C and Apo E groups are present in all types of lipoprotein except LDL. Specification, page 2.

"Many epidemiological and clinical studies have shown that increased LDL levels in the blood are associated with increased risk of CHD [coronary heart disease]." Page 4. "In contrast . . ., individuals with high concentrations of HDL . . . seldom express symptoms of CHD." Page 5. The specification discloses "antibodies immunoreactive with specific epitopes on lipoproteins, such as those on LDL, VLDL and HDL, that enable rapid and reliable determinations of levels of lipoproteins and/or apolipoproteins in whole blood, serum or plasma." Page 14.

In particular, the specification discloses that "[c]onventional ways of producing MAbs [monoclonal antibodies] to Apo B-100 include immunization of mice with LDL. . . . However, MAbs produced using LDL as an immunogen tend to be sensitive to conformational changes of Apo B-100 caused by variations in the lipid composition of LDL particles." Page 26. "To obtain an anti-LDL MAb whose binding to LDL particles is not dependent on variations in LDL composition and/or conformation, mice were immunized with soluble Apo B-100 which had been delipidized, reduced, carboxymethylated and, purified by electrophoration in polyacrylamide gels containing 8 M urea (Lee, D.M. et al., Biochim. Biophys. Acta, 666:133-146 (1981))." Id., page 27.

"The spleen cells of mice that were immunized using the soluble and electrophoretically purified Apo B, were then used to produce hybridomas according to standard hybridoma methods." Id. One of the resulting monoclonal antibodies was designated HB_3cB_3. Id. "HB_3cB_3 binds to the epitope near the T2 carboxy terminal region of B-100, exclusively, and does not recognize B-48. The epitope recognized by HB_3cB_3 may be conformationally changed or masked by lipids and/or other apolipoproteins present in VLDL." Id. Thus, monoclonal antibody HB_3cB_3 binds exclusively to LDL.

Discussion

Claim 48, the only independent claim, is directed to a method for making antibodies that will react with a lipoprotein regardless of lipid content and conformation of the lipoprotein, by treating a lipoprotein or apolipoprotein to delipidate, reduce, carboxymethylate, and solubilize it with a reducing or denaturing agent, removing all self-aggregated and degraded material, and immunizing an animal with the treated apolipoprotein.

The examiner rejected claim 48, together with dependent claims 49-52, as containing new matter, i.e., lacking an adequate description in the specification. The examiner summarized her position as follows:

> The entire written description support for these method claims [is] provided for on page 27, lines 5-16 (Example 2) and page 47, lines 15-34. . . . These passages do not provide for conception and written description support for that which is now broadly claimed because [they] do not provide conception by way of written description for (a) immunizing with lipoproteins or generic apolipoproteins so treated; (b) antibodies in general/polyclonal antibodies; (c) subgenus of reducing or denaturing agents; (d) immunization [with] soluble lipoprotein or apolipoprotein

> produced by the method; and (e) generic means of removal of all self-aggregated and degraded material.

Examiner's Answer, page 6. The examiner further explained these points on pages 6-11 of the Answer.

Appellants argue that the specification's description satisfies 35 U.S.C. § 112, first paragraph:

> The application has a long discussion of all of the various known apolipoproteins and which lipoproteins they form. The application describes how to specifically delipidated [sic], reduce, carboxylate [sic, carboxymethylate], and isolate antigen, as well as how to immunize animals, obtain polyclonal antibodies, and screen for the desired specificity. The application demonstrates how to make monoclonal antibodies, and recombinant antibodies with the same specificity. Nothing more is required.

Appeal Brief, page 8.

The examiner "'bears the initial burden . . . of presenting a prima facie case of unpatentability.' In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Insofar as the written description requirement is concerned, that burden is discharged by 'presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.' . . . If . . . the specification contains a description of the claimed invention, albeit not in ipsis verbis (in the identical words), then the examiner . . ., in order to meet the burden of proof, must provide reasons why one of ordinary skill in the art would not consider the description sufficient." In re Alton, 76 F.3d 1168, 1175, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

"In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide in haec verba support for the claimed subject matter at

issue." Purdue Pharma L.P. v. Faulding, Inc., 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000). Nonetheless, the disclosure must convey with reasonable clarity to those skilled in the art that the inventor was in possession of the invention. See id.

The examiner set out five aspects of the claimed method that, in her opinion, were not adequately described in the specification. The examiner argues that the claims contain new matter because they are not limited to monoclonal (as opposed to polyclonal) antibodies; because they are not limited to the electrophoretic purification method disclosed in the specification; because they are not limited to the specific solubilization method used in the specification; because they read on immunizing an animal with a soluble lipoprotein, in addition to soluble apolipoprotein; and because the immunogen administered in the specification was not in soluble and reduced form because it was administered while still in a polyacrylamide gel (and therefore insoluble) and the specification does not disclose that the gel contained a reducing agent.

We agree with Appellants that none of the claim limitations pointed to by the examiner render the specification's description inadequate. We agree with Appellants' arguments that

> [w]ith respect to . . . polyclonal antibodies, immunization of an animal with an antigen will always produce polyclonal antibodies. One must then isolate spleen cells and fuse these with immortal cells, which are then screened, for production of monoclonal antibodies.
>
> With respect to the issue of "lipoprotein" versus "apolipoprotein", any one skilled in the art would understand that when one delipidates a lipoprotein, one by definition obtains an apolipoprotein. It is therefore irrelevant whether one starts with a lipoprotein or an apolipoprotein, one will utilize the same material as an antigen.

Appeal Brief, page 6. The examiner did not adequately rebut these arguments.

The examiner also objected to the claims' recitation of "solubiliz[ation] with a reducing or denaturing agent." See the Examiner's Answer, page 8: "The [relevant] passage [in the specification] does not specify how the ApoB-100 was solubilized and thus the amendment to provide solubilization with a reducing or denaturing agent provides a new subgenus of agents that is not supported by the original written description."

We do not agree with the examiner's reasoning. Whether a specification adequately describes a later-claimed invention is determined from the viewpoint of those of skill in the art. See, e.g., Eiselstein v. Frank, 52 F.3d 1035, 1039, 34 USPQ2d 1467, 1470 (Fed. Cir. 1995) ("The test is whether the disclosure of the application relied upon reasonably conveys to a person skilled in the art that the inventor had possession of the claimed subject matter at the time of the earlier filing date."). Here, the specification cites the Lee reference as the basis of the protocol used to solubilize Apo B-100. In addition, the examiner has provided no basis for concluding that those skilled in the art would not have been aware of reducing and denaturing agents, other than those used by Lee, that were commonly used to solubilize proteins. Thus, the examiner has not carried her burden of showing that the specification did not convey possession of this aspect of the method now claimed to a person of skill in the art.

The same is true of the examiner's concern regarding "generic means of removal of all self-aggregated and degraded material." Examiner's Answer, page 6. The specification describes purification by gel electrophoresis, Lee describes purification by gel filtration chromatography (page 136), and the examiner has provided no basis for concluding that those skilled in the art would not have been aware of other, equally

applicable methods of separating a reduced, carboxymethylated, and solubilized apolipoprotein away from self-aggregated and degraded material.

Finally, the examiner argues that the specification does not describe the claimed method because the Apo B-100 used as the immunogen in the specification was not soluble, since the protein was not removed from the polyacrylamide gel matrix before being injected into mice (and therefore was insoluble). We do not share this concern: both the specification (see page 27) and the Lee reference (see the abstract) make clear that those skilled in the art understood that the method steps recited in the claims produce "soluble" Apo B-100. That the soluble protein was then electrophoresed in a polyacrylamide gel does not change the soluble protein into an insoluble one; if the protein was removed from the gel, the skilled artisan would still expect the protein to be soluble in aqueous media. That is, those skilled in the art would understand the specification to describe a process of immunizing mice with a soluble protein, together with an insoluble polyacrylamide gel matrix.[1]

We conclude that the examiner has not established that those skilled in the art would not recognize the specification's description to show possession of the method now claimed. The rejection under 35 U.S.C. § 112, first paragraph, is reversed.

New Grounds of Rejection

Under the provisions of 37 CFR § 41.50(b), we enter the following new grounds of rejection: claim 48 is rejected under 35 U.S.C. § 102(b) as anticipated by Lee, and

[1] Along the same line, the examiner argues that the Apo B-100 immunogen was not in a reduced form when it was injected, since the specification does not indicate that the polyacrylamide gel used to separate the intact Apo B-100 from self-aggregated and degraded material contained any reducing agent. This argument is addressed in the new grounds of rejection, below.

claims 49-51 are rejected under 35 U.S.C. § 103 as obvious in view of Lee and Goding.[2]

Lee teaches a method of making an antibody to LDL. Lee describes the preparation of the immunogen as follows: "The LDL_2 were delipidized wet with ethanol and diethyl ether, the latter being freed of peroxides before use. The LDL_2 apolipoprotein obtained was solubilized totally in 6 M guanidine HCl buffer containing the reducing agent dithiothreitol. After carboxymethylation, the reduced and carboxymethylated (RCM) LDL_2 apolipoprotein was purified by gel filtration to yield pure RCM apolipoprotein B." Abstract. The RCM apolipoprotein B was then used to immunize a rabbit (page 136, right-hand column).

Thus, Lee teaches a method of making antibodies comprising immunizing an animal with a desired apolipoprotein that has been delipidated, reduced, carboxymethylated, and solubilized with a reducing or denaturing agent (guanidine HCl buffer containing dithiothreitol), where all self-aggregated and degraded material have been removed from the treated apolipoprotein (by gel filtration). Thus, the method taught by Lee meets all the limitations of claim 48.

Lee does not teach a method of making monoclonal antibodies, as in instant claim 49. However, Goding teaches methods of making monoclonal antibodies to a desired antigen. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the delipidated, reduced, carboxymethylated, and solubilized apolipoprotein taught by Lee as the antigen in Goding's method of making monoclonal antibodies. Motivation to combine the references is provided by Lee, which

[2] Goding, Monoclonal Antibodies: Principles and Practice, pp. 56-97, Academic Press, Inc. (1983).

teaches that the apolipoprotein that Lee used to raise antibodies is the major protein component of LDL, which is the principal carrier of cholesterol in the circulation (page 134, left-hand column); antibodies to the apolipoprotein would therefore have been expected to be useful in quantitating serum LDL levels.

Those skilled in the art would have been motivated to use Goding's methods of making monoclonal antibodies because such methods allow "a virtually unlimited supply of identical antibodies." Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1369, 231 USPQ 81, 82 (Fed. Cir. 1987). Thus, the method of claim 49 would have been obvious to those skilled in the art at the time of the invention. Lee's method involves making antibodies to Apo B, which will bind to LDL; the combination of Lee and Goding therefore meets all the limitations of claims 50 and 51.

The above rejections are basically the same as those made earlier in prosecution by the examiner. See the Office action mailed January 30, 2001. In response to these rejections, Appellants argued that Lee's method differs from the one claimed because Lee "does not immunize an animal with the delipidated, decarboxymethylated [sic], reduced apolipoprotein. He has removed the reducing agents from the apolipoprotein. In contrast, . . . applicants immunized with the delipidated, decarboxymethylated [sic], reduced apolipoprotein from which the degraded and complexed materials had been removed." Appellants' response to the Final Office action, received September 4, 2001.

The examiner withdrew the prior art-based rejections, but we believe they should have been maintained. The fact that Lee removed the reducing agent from the apolipoprotein preparation by dialyzing against distilled water is immaterial because the apolipoprotein had been modified by carboxymethylation after it was reduced. Lundblad

discusses carboxymethylation of proteins.[3] See, e.g., Lundblad's Figure 2: treatment of a protein with a reducing agent like dithiothreitol breaks the disulfide bonds that normally exist between certain cysteine residues; thus, each –S—S– bond becomes two –SH groups (the starting point of the reaction in Lundblad's figure). Each –SH group can then be carboxymethylated, converting it to an $–S–CH_2–COOH$ moiety.

Lundblad states that blocking the sulfhydryl (–SH) groups by, e.g., alkylation prevents them from reoxidizing to re-form disulfide bonds. See page 95. Thus, carboxymethylation prevents the protein from resuming its original, oxidized state; after carboxymethylation, the original –S—S– bond cannot reform even if the reducing agent is removed.

For this reason, the fact that Lee removed the reducing agent from the reduced and carboxymethylated Apo B does not distinguish the method disclosed by Lee from the one claimed by Appellants. Both processes involve immunizing an animal with reduced, carboxymethylated, solubilized, and purified apolipoprotein. Lee therefore anticipates claim 48; combined with Goding, it would have made obvious claims 49-51.

Summary

The specification adequately describes the claimed process; Lee also describes the process of claim 48 and, combined with Goding, it would have made obvious the process of claims 49-51. We therefore reverse the examiner's rejection and enter two new grounds of rejection.

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[3] Lundblad et al., Chemical Reagents for Protein Modification, Volume I, pp. 55-60 and 95-98, CRC Press (1984), copy enclosed. We cite Lundblad only as evidence of how Lee would have been understood by those skilled in the art. Lundblad's disclosure is not necessary to reach any limitation of the claims on appeal.

Time Period for Response

This decision contains a new ground of rejection pursuant to 37 CFR § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 CFR § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 CFR § 41.50(b) also provides that the appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

> (1) *Reopen prosecution.* Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the proceeding will be remanded to the examiner. . . .
>
> (2) *Request rehearing.* Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

REVERSED, 37 CFR § 41.50(b)

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Administrative Patent Judge)
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